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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/360,685	07/26/99	COVACCI A	CHIR-0157

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EXAMINER	
BUI, P	
ART UNIT	**PAPER NUMBER**
1638	15

DATE MAILED: 10/24/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/360,685	Covacci et al.
Examiner	**Group Art Unit**
Phuong Bui	1638

☒ Responsive to communication(s) filed on *Aug 7, 2000*.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *38-42, 44, 45, 47, 48, 50, 51, 53, 54, 56, 57, and 59-70* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☒ Claim(s) *40 and 41* is/are allowed.

☒ Claim(s) *38, 39, 42, 44, 45, 47, 48, 50, 51, 53, 54, 56, 57, and 59-70* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☒ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☒ received in Application No. (Series Code/Serial Number) *08/256,848*.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *6*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

1. The Office acknowledges the receipt of Amendment C, Paper No. 12, filed August 7, 2000, and the executed Declaration under 37 C.F.R. §1.132 of Giuseppe Del Giudice filed August 25, 2000. Claims 43, 46, 49, 52, 55 and 58 have been cancelled. New claims 66-70 have been entered. Accordingly, claims 38-42, 44, 45, 47, 48, 50, 51, 53, 54, 56, 57 and 59-70 are pending and are examined in the instant application.

Information Disclosure Statement

2. An initialed copy of Applicant's form 1449, filed February 28, 2000 (Paper No. 6) is attached to this Office action. However, since the Figura et al. document was not submitted, this document has not been considered.

Drawings

3. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

Specification

4. Applicant's correction of the continuity data and insertion of SEQ ID NOs in the specification have been entered. The abstract has been entered. Accordingly, the objection to the specification set forth in the previous Office Action, Paper No. 3, mailed February 14, 2000, has been overcome by Applicant's corrections.

5. Claims 67 and 69 are objected to as neither claim contains a period at the end thereof. Correction is required.

Sequence Compliance

6. Applicant's sequence submission of August 7, 2000 is compliant and has been entered.

35 U.S.C. 112, second paragraph

7. The rejection of claims 42-65 under 35 U.S.C. 112, second paragraph, has been overcome by Applicant's response. In accordance with the meaning recited in the Declaration of Giuseppe Del Giudice under 37 C.F.R. §1.132 filed August 25, 2000, "substantially reduced functional contribution to toxicity" will be read to mean no "statistically significant cytotoxic effects" (Declaration, page 3, paragraph 7).

35 U.S.C. 112, first paragraph

8. The new matter rejection of claims 42-65 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonable convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention has been overcome by Applicant's response.

9. Claims 48, 50, 51, 53, 54, 56, 57, 59, 60-65 and 70 are rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for the *H. pylori* cytotoxin associated immunodominant (CAI) antigen and non-toxic immunogenic fragments thereof, does not reasonably provide enablement for the prophylactic or therapeutic vaccine, nor the methods

for making and using this vaccine. The basis for this rejection was set forth in the previous Office action, Paper No. 3, mailed February 14, 2000.

The Declaration of Giuseppe Del Giudice under 37 C.F.R. §1.132 filed August 25, 2000 has been fully considered, but was not found persuasive. Applicant should note that the declaration was found persuasive to the extent that determination of immunogenic fragments that were also non-toxic would have been within the skill in the art. However, with regard to the determination of vaccine efficacy, especially for prophylactic administration, the declaration was unpersuasive in that the showings set forth therein are not commensurate in scope with the specification.

Initially, declarant asserts that animal models for the study of infection were known prior to March 2, 1992, the filing date of Applicant's Italian priority document. Declarant also establishes the existence of immunological assays to screen for antibody production in response to immunizations with CAI protein fragments. For the record, the Office avers to the existence of animal models for the study of *H. pylori* infection and to the existence of immunological screening assays for determining immunogenic fragments. Declarant has established that determination of non-toxic, immunogenic fragments of the CAI antigen was well within the skill of the art at the time of the invention.

However, the existence of animal models does not support declarant's conclusion that these animal models would allow determination of prophylactic or therapeutic effect to be

routinely carried out. Such a conclusion is unsupported on the record for the following reasons. Declarant's Exhibit E reviews animal models of *H. pylori* infection and their use in vaccine studies. This exhibit actually contradicts Declarant's conclusion. On pages 247 and 248, section 2.8.3, the author indicates that the initial assumption in *H. pylori* studies was that gastric IgA antibodies probably played a major role in preventing or clearing *H. pylori* based on knowledge from other mucosal pathogens. The author continues by stating that protection from *H. pylori* can actually occur in the absence of any antibodies, indicating that T-cells may play a role in protection from *H. pylori* infection. These two facts contradict Declarant's conclusion that vaccine studies were routine at the time of the invention, especially in light of the recent 1999 publication date of this review article. This problem would be present for both the full length CAI antigen and any non-toxic, immunogenic fragments thereof.

The fragments present an additional problem not seen in with the full length antigen. Even if Applicant were able to show that the full length antigen is capable of preventing or clearing *H. pylori* infection, discovery of the protective epitope or epitopes would still be highly unpredictable and involve extensive, undue experimentation. Although screening for linear epitopes was considered to be routine at the time of the invention, screening for non-linear epitopes was not. To discover non-linear epitopes, it is necessary to analyze the 3-dimensional structural conformation of the antigen as well as it's amino acid sequence. Moreover, many vaccines

require multiple epitopes, even multiple antigens to provide protection. Thus, the discovery of protective epitopes is therefore highly unpredictable.

Exhibit F discusses vaccines using a detoxified form of the CAI antigen that provided significant clearance and protection in a mouse model. These vaccines included a mucosal adjuvant and included a detoxified form of the full length antigen. Exhibit G discusses vaccines which also provided significant clearance and protection in a dog model. These vaccines included a mixture of recombinant, full-length CAI antigen with the cytotoxin VacA and NAP in addition to aluminum hydroxide as the adjuvant. Administration was via intramuscular vaccination. Though these two references demonstrate the vaccine potential of the CAI antigen, they fail to support the enablement of the claimed invention. Both references include ingredients and protocols not discussed in the specification. Both references are post-filing documents. The use of post-filing documents cannot support enablement of a claimed invention unless the teachings of these documents follow the teachings of the specification. Accordingly, these two documents fail to support enablement of the claimed invention, even with regard to a detoxified form of the full-length CAI antigen. Additionally, though the CAI antigen has been shown to have vaccine potential, neither document provides any support whatever for protective non-toxic, immunogenic fragments within the scope of the claims.

Applicant's response filed August 7, 2000 has been fully considered, but was not found persuasive. Applicant asserts that there is insufficient evidence to support this rejection. In

accordance with the 35 U.S.C. §112, first paragraph, enablement guidelines of August 1996, evidentiary support for a 35 U.S.C. §112, first paragraph, scope of enablement rejection may be provided in either references or scientific reasoning. To the extent that this rejection was founded on scientific reasoning, the references now submitted by Applicant in support of the 37 C.F.R. §1.132 declaration in fact bear out this reasoning. For example, the previous action indicates that a mucosal adjuvant is required for vaccine efficacy of *H. pylori* component vaccines. In Exhibit F, the inventors with others administered a CAI antigen in admixture with a known mucosal adjuvant via a mucosal route of administration. As was already discussed above, Exhibit E, a 1999 review article indicates that "[b]ased on knowledge from other mucosal pathogens, the initial assumption in *Helicobacter* vaccine studies was that gastric IgA antibodies probably played a major role in preventing or clearing *Helicobacter* infections." (Exhibit E, page 247, section 2.8.3). Exhibit G confirms this approach on page 5, lines 30-32 to page 6, lines 1-12. Exhibit G, filed by the instant assignee, indicates that a systemic protective effect against *H. pylori* infection can be "unexpectedly" achieved using a non-mucosal route of administration and non-mucosal adjuvant (Exhibit H, page 6, lines 13-20). Thus, the effects of *in vivo* administration were poorly understood until recently, and certainly at the time of filing of this invention.

Finally, the Office declines Applicant's request for an affidavit under 37 C.F.R. §1.104(d)(2), as such is not deemed necessary given the current record.

35 U.S.C. 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The rejection of claims 38, 39, 42, 44, 45, 47, 48, 50, 54, 56, 66, and 68 under 35 U.S.C. 102(e) as being anticipated by Applicant's admitted prior art Cover et al. (Infection and Immunity, Mar 1990, Vol. 58, No. 3, pp. 603-610) is maintained for reasons set forth in the previous Office Action.

The Declaration of Giuseppe Del Guidice filed August 25, 2000 under 37 C.F.R. §1.132 has been fully considered, but was not found persuasive with regard to the remaining claims under this rejection. This declaration will be addressed only with regard to the assertions made regarding these remaining rejected claims. Specifically, Declarant states that Cover et al. did not purify the 128 kDa *H.pylori* protein. No support is given for this statement. However, Cover did in fact purify the CAI antigen in that the antigen was first present in a concentrated culture supernatant. The term "purified" is normally read to mean "that at least one step of purification has been carried out such that a purified antigen is more pure than the same antigen in its natural context." (Exhibit F, page 7, lines 14-17). The instant specification however defines purified to mean that the antigen "is present in the substantial absence of other biological macromolecules of

the same type." (Specification, page 16, lines 19-22). This definition has two problems: (1) the term "substantial" has not been defined; and (2) the Specification, page 7, line 27 uses the terms "same type" to refer to the same molecule being purified. The first problem is one of percentage of the purified antigen. The second problem shows that there exists an internal inconsistency in the definition. Since the definition provided by the Specification is ambiguous, the meaning that must be taken for the term "purified" is one consistent with the art recognized meaning as set forth in Exhibit G. Clearly the concentrated culture supernatant reads on the Exhibit's definition in that at least one step is performed to concentrate the antigen.

With regard to the claim requirement that the CAI polypeptide exhibit no functional or statistically significant contribution to toxicity, it should be noted that this protein does not possess the cytotoxicity of the VacA cytotoxin. Accordingly, any fragment, including the full length CAI antigen would exhibit no functional or statistically significant contribution to toxicity.

35 U.S.C. 103(a)

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. The rejection of claims 60 and 62 under 35 U.S.C. 103(a) as being unpatentable over Cover et al. is maintained for the reasons set forth in the previous Office action.

Applicant's arguments with regard to this rejection have been fully considered, but were not found persuasive. Applicant asserts that an "aqueous medium" such as the phosphate buffered saline used in Cover et al. is not an inherently pharmaceutical carrier. However, water is commonly used to as a delivery vehicle and solvent for delivery of oral as well as injectable medicines, especially for proteinaceous medicines. Accordingly, one skilled in the art would have found the use of an aqueous carrier to have been obvious at the time of the instant invention as a means for storing the concentrated culture supernatant.

Remarks

13. Claims 40, 41, and 70 define over the prior art of record.

14. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed untile after the end of the THREE MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Papers relating to this application may be submitted to Technology Sector 1 by facsimile transmission. Papers should be faxed to Crystal Mall 1, Art Unit 1638 using fax number (703) 308-4242. All Technology Sector 1 fax machines are available to receive transmissions 24 hrs/day, 7 days/wk. Please note that the faxing of such papers must conform with the Notice published in the Official Gazette, 1096 OG 30, (November 15, 1989).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Bui whose telephone number is (703) 305-1996. The Examiner can normally be reached Monday-Friday from 6:30 AM - 4:00 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Paula Hutzell, can be reached at (703) 308-4310.

Any inquiry of a general nature or relating to the status of this application should be directed to the receptionist whose telephone number is (703) 308-0196.

Phuong Bui
Patent Examiner
Group Art Unit 1638
October 22, 2000

PHUONG T. BUI
PRIMARY EXAMINER